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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	MANIKANDAN*et al.*	Atty. Dkt. No.:	RLL-278US
Serial No.:	10/523,116	Group Art Unit:	1645
Filing Date:	March 10, 2006	Examiner:	Unknown

Title: PROCESS FOR THE PREPARATION OF DISPERSIBLE TABLETS OF CEPHALEXIN

Certificate of Mailing

I certify that this correspondence is being deposited with the United States Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on November 14, 2006.

Kim Campbell

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 815/Del/2002 filed 2 August 2002 (02.08.2002) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: _____
Jayadeep R. Deshmukh
Vice President - Intellectual Property

Dated: November 14, 2006

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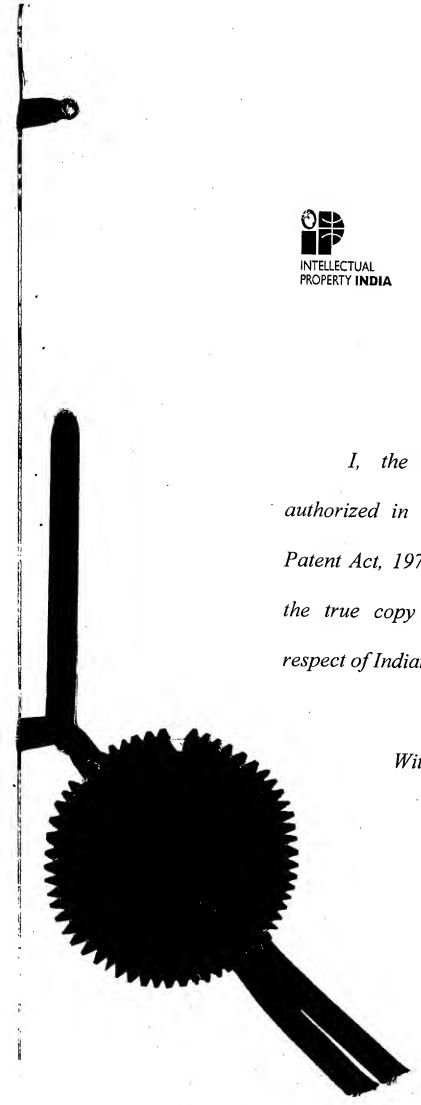

INTELLECTUAL PROPERTY **INDIA**

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI
BOUDHIK SAMPADA BHAWAN,
PLOT NO. 32, SECTOR – 14,
NEW DELHI - 110 075.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of ***Application*** *and* ***Specification*** *in respect of Indian Patent No.* ***194821 (815/Del/2002)****.*

Witness my hand this 21st day of July 2006.

CERTIFIED COPY OF
PRIORITY DOCUMENT

(P.K. PATNI)
Deputy Controller of Patents & Designs

0815-2

02 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1. We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF DISPERSIBLE TABLETS OF CEPHALEXIN"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. R. MANIKANDAN
b. ASHISH GOGIA
c. SUNILENDU BHUSHAN ROY
d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, R. MANIKANDAN, ASHISH GOGIA, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(R. MANIKANDAN)

b.

(ASHISH GOGIA)

c.

(SUNILENDU BHUSHAN ROY)

d.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683404** dated **20.07.2002** on **ANZ Grindlays Bank, New Delhi**.

We request that a patent may be granted to us for the said invention.

Dated this **2ND** day of **AUGUST, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

THE PATENT OFFICE

2ND M.S.O. BUILDING

234/4, ACHARYA JAGADISH CHANDRA BOSE ROAD

KOLKATA – 700 020.

INTELLECTUAL PROPERTY INDIA

INDIAN PATENT SPECIFICATION

(51) Int. Cl. : A 61K 47/00, 31/79 & 9/20	A	(11) Document No. IN
		Date of Document : 02/8/2002
(52) Ind. Cl. : 55 E4		(42) Date of Publication :
(21) Application No. : 815/DEL/2002		(71) Applicant : Ranbaxy Laboratories Limited, of 19, Nehru Place, New Delhi - 110 019, India.
(22) Date of filing : 02/08/2002		**(72) Inventor :-** RAMALINGAM - MANIKANDAN - INDIAN
		ASHISH - GOGIA - INDIAN
		SUNILENDU BHUSHAN ROY - INDIAN
		RAJIV - MALIK - INDIAN
(33) Country : ..		
(32) Date : ..		
(31) Number : ..		
Claims : 17		Examiner : Monica Yadav
Text : No of pages : 15 No. of Drawing Sheets : NIL		

(54) Title : "A process for the preparation of water dispersible tablets of cephalexin".

(57) Abstract : A process for the preparation of water dispersible tablets of cephalexin, which disintegrate within 3 minutes in water at 20°C±5°C to form a uniform suspension wherein the process comprises granulating cephalexin, conventional intragranular disintegrant(s) and colloidal silicon dioxide and optionally suspending/coloring agent with binder solution, of the kind as herein described; drying the resulting granules, mixing with conventional extragranular disintegrant(s), fillers, lubricating agents and optionally other excipients and compressing to form tablets; wherein the disintegrant comprises from 0.5% to 10%; colloidal silicon dioxide comprises from 0.25% to 6.0%; and binder comprises 0.25% to 4%; and lubricant comprises from 0.25% to 5% by weight of the total tablet weight.

Reference : Reference has been made to US Patent No. 4886669 & 5955107.

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see

FORM – 2

THE PATENTS ACT, 1970

COMPLETE

SPECIFICATION

SECTION 10

The following specification particularly described and ascertain the nature of this invention and the manner in which it is to be performed :-

The present invention relates to a process for the preparation of water dispersible tablets of cephalexin.

Cephalexin [7-(D-α-Amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid] belongs to the class of cephalosporin β-lactam antibiotics. It is a semisynthetic cephalosporin antibiotic intended for oral administration. Cephalexin has been shown to be active against a variety of gram positive and gram negative bacteria. Presently, cephalexin is available as capsules, tablet and dry syrup.

The major drawback for tablet dosage form is that they are large in size and often pose problem of swallowing by pediatric and geriatric patients. Further there is also the problem of dissolution and disintegration with these tabletted formulations, which is a prerequisite of any formulation to achieve effective plasma concentration. The absorption of a medicament from any dosage form should be fast and predictable. The suspension formulations have been found to be better candidates for rapid absorption of drugs and as compared to tablets.

Dry syrups have to be reconstituted with water before ingestion. These are sometimes bulky and need careful measurement of vehicle, which is not always conducive and convenient. Normally, suspensions are to be refrigerated to prevent the loss of potency and therefore are inconvenient while traveling. Further, they require skills for precise and correct measurement of dose.

Water dispersible tablets provide solution to the above problems. Prior art describes the composition and method of preparation of dispersible tablet of amoxicillin and cefaclor antibiotics.

For example, US Pat. No. 4,950,484 describes a dispersible tablet of amoxicillin comprising a mixture of microcrystalline cellulose and low substituted hydroxypropyl cellulose as disintegrant.

Similarly US Pat. No. 5,681,141 describes preparation of dispersible tablets of cefaclor by direct compression comprising a disintegrant, and sodium stearyl fumarate as lubricant.

US Pat. No. 5,861,172 provides a process for the manufacture of a tablet in which granules comprising a compacted mixture of amoxicillin, together with an intra-granular disintegrant are mixed with an extra-granular disintegrant to form a tablet.

US Pat. No. 5,837,292 provides a granulate comprising beta-lactam antibiotic in admixture with a water dispersible cellulose such as microcrystalline cellulose and sodium carboxymethylcellulose.

US Pat. No. 5,955,107 describes the pharmaceutical suspension tablet comprising antibiotics, croscarmellose sodium, microcrystalline cellulose and coprocessed additive consisting essentially of microcrystalline cellulose and calcium, sodium alginate complex

US Pat. No. 4,886,669 discloses a water dispersible tablet consisting of coated microparticles of antibiotics, disintegrant and a swellable material.

None of the above prior art provides a simple and easy method of manufacturing a water dispersible dosage form of cephalexin in particular. Further, the primary requisite

of a dispersible tablet is that it should rapidly disintegrate in water, forming a uniform suspension that has smooth mouth feel without any gritty particles.

In the present invention we have surprisingly discovered that water dispersible tablets of Cephalexin, which disintegrate within 3 minutes in water at 20 °C± 5 °C to form a uniform suspension of cephalexin can be easily prepared by wet granulation method using optimum amount of disintegrant, colloidal silicon dioxide and binder.

Accordingly the object of the present invention is to provide a process for the preparation of water dispersible tablets of cephalexin, which disintegrate within 3 minutes in water at 20°C± 5°C to form a uniform suspension wherein the process comprises granulating cephalexin, conventional intragranular disintegrant(s) and colloidal silicon dioxide and optionally suspending/coloring agent with binder solution, of the kind as herein described; drying the resulting granules, mixing with conventional extragranular disintegrant(s), fillers, lubricating agents and optionally other excipients and compressing to form tablets; wherein the disintegrant comprises from 0.5% to 10%; colloidal silicon dioxide comprises from 0.25% to 6.0%; and binder comprises 0.25% to 4%, and lubricant comprises from 0.25% to 5% by weight of the total tablet weight.

Another object of the present invention is to provide a process for the preparation of water dispersible tablet of cephalexin wherein a mixture of cephalexin, disintegrant and colloidal silicon dioxide are granulated with binder solution, resulting granules

are dried, mixed with disintegrants, fillers, lubricating agents and optionally other excipients, and then compressed to form tablets.

Granules of the present invention in addition to cephalexin, disintegrant(s), colloidal silicon dioxide and binder may also comprise suspending agents and or coloring agent. Other excipients may be selected from antiadherants, sweeteners, coloring agents and flavoring agents.

The dispersible tablets of the present invention readily disperse in water in less than three minutes and give a uniform suspension, which is free of grittiness and lumps. Suspension formed by dispersing two tablets in 100ml of water has a particle size distribution of d_{90} less than 600 μm and Cephalexin particles remain suspended for a sufficient period of time for easy dosing.

For the purpose of present invention Cephalexin is present as cephalexin monohydrate. The particle size of cephalexin used in accordance with the present invention was reduced to d_{90} less than 250 μm. The amount of cephalexin may vary from about 20% to about 50% by weight of the total tablet weight.

The disintegrants of the present invention may be selected from the group consisting of sodium starch glycolate, carboxy methylcellulose, croscarmellose sodium and crospovidone or combinations thereof. The disintegrant may be used in an amount from about 0.5% to about 10% w/w. The intragranular and extragranular disintegrant may be same or different. The preferred disintegrant is crospovidone.

Binder of the present invention may be selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone (povidone) or combinations thereof. The binder of the present invention may be present in an amount from about 0.25% to 4% by weight of the total weight of tablet. The preferred choice is polyvinylpyrrolidone. The ratio of the amount of disintegrant to the amount of binder is crucial for obtaining fast dispersing tablets having less friability. For the purpose of the present invention ratio of the amount of disintegrant to the amount of binder may vary from 1:1 to 1:20 depending upon the disintegrant and binder used. However, 1:5 to 1:15 gives the best results.

The fillers of the present invention may be selected from the group consisting of lactose, microcrystalline cellulose, mannitol or combinations thereof. The preferred diluent is microcrystalline cellulose, which also acts as a binder and disintegrant by virtue of its swelling properties. Various types of commercially available microcrystalline cellulose can be used, preferred choice is, but not limited to, AVICEL PH 101 having average particle size of about 50 microns or AVICEL PH 302 having average particle size of about 90 microns.

The suspending agent of the present invention may be selected from the group consisting of microcrystalline cellulose, sodium carboxy methyl cellulose, colloidal silicon dioxide, mannitol, povidone, sodium starch glycolate, veegum or a combination thereof.

The lubricants of the present invention may be selected from the group consisting of magnesium stearate, stearic acid or sodium stearyl fumarate and combinations

thereof. The preferred choice is magnesium stearate. The lubricant may be used in an amount of about 0.25% to about 5% by weight of total tablet weight.

For the purpose of this invention, colloidal silicon dioxide also includes colloidal silica or its derivatives such as Syloid. Colloidal silicon dioxide serves two purposes, first as antiadherant and then as a suspension aid. It can be used intragranularly as well extragranularly. The preferred amount is from about 0.25% to about 6.0% by weight of the total tablet weight.

Sweeteners for the present invention may be selected from sugars, saccharin or its salts, aspartame or combinations thereof. The amount used may depend upon the sweetener used. The preferred sweetener is aspartame at about 0.01% to about 2.0% by weight of the total tablet weight.

As for flavoring agents, any flavoring agent approved by FDA for oral use may be used. The preferred flavors are "Flavor Peppermint" and "Flavor fruit gum". The preferred range of flavoring agent is from about 0.1 to 4.0% by weight of the total formulation weight.

Colorants impart aesthetics and the preferred choice is D&C Yellow Aluminum Lake at less than 1% w/w of the formulation. These may be used intragranularly as well as extragranularly.

Dispersible tablet of the present invention may be best prepared by wet granulation method as it results in more porous granules which help in rapid disintegration.

Particle size of the excipients is very important for a suspension (made from dispersible tablet) to have a smooth mouth feel. As per British Pharmacopoeia also the particles of a suspension should pass through a 600 μm sieve, without leaving any residue. A suspension complying with this requirement can, however, still have a gritty mouth feel. It is preferable, therefore to have finer suspension containing a more uniform size particles. The dispersible tablets made in accordance with the present invention forms a uniform dispersion upon swirling which has a smooth mouth feel and is free of gritty particles. The particle size distribution in the suspension was d_{90} less than 600μm.

Cephalexin, colloidal silicon dioxide, coloring agent and disintegrant are sifted. Sifted cephalexin, color (half quantity), disintegrant (half quantity) are mixed in a Rapid Mixer Granulator. Binder is sifted and is dissolved in measured quantity of Purified Water using a mechanical stirrer. The premix is then wet granulated with binder solution in a rapid mixer granulator. The granules are dried in Fluidized bed dryer at 60°±5°C. The dried granules are sifted through mesh 22 BSS (699 μm) and collected. Fillers, antiadherant, colorant and disintegrant are sifted and mixed in a non-shear blender. The dried granules are then mixed with premix of filler, antiadherant, colorant and disintegrant in a non-shear blender for 20 minutes. Sweetener, flavor are sifted through mesh 60 BSS (251 μm) sieve added to the above blend and mixed for 5 minutes. Finally lubricant is added and blended for 10 minutes and blend is then compressed with appropriate tooling to make tablets.

Dispersible tablets of the present invention have the advantages of conventional tablets and capsules in terms of accuracy of dosing and ease of handling, and of

suspensions for better bioavailability and more patient compliance in case of younger, elderly and patients who have difficulty in swallowing. These tablets have low friability and therefore are easily transportable. No refrigeration is required as in case of suspension. The dispersible tablets of the present invention are meant to, but are not limited to, form a suspension and therefore can also be administered as conventional tablet. Also the granules, that are compressed to form these tablets, can be used to form rapidly disintegrating chewable tablets or lozenges.

The following example illustrates specific implementation of the invention and should not be construed as limiting it.

EXAMPLE

COMPONENT	WEIGHT (mg)	% by weight
Intragranular		
Cephalexin	264.02	33.00
Crospovidone	12.00	1.50
Colloidal silicon dioxide	12.0	1.50
Povidone	4.00	0.50
D&C Yellow 10 aluminum lake	0.26	0.0325
Purified water	qs	qs
Extragranular		
Mannitol	180.0	22.50
Microcrystalline cellulose	254.72	31.84
Crospovidone	36.00	4.50
Aspartame	10.00	1.25
Flavour Peppermint 517	2.00	0.25
Flavor Fruit Gum 912	10.00	1.25
D&C Yellow 10 aluminum lake	1.00	0.125
Colloidal silicon dioxide	4.00	0.50
Magnesium stearate	10.00	1.25

Process:

Cephalexin, crospovidone, color and colloidal silicon dioxide are mixed and granulated with an aqueous solution of povidone. The resulting granules are mixed with microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and mannitol

for 20 minutes. To this blend are added aspartame, D&C yellow 10 Aluminum Lake, magnesium stearate, flavour peppermint 517 and flavour fruit gum 912. The final blend is then compressed.

The tablets made as per the above example were subjected to accelerated stability studies at 40°C/75%RH, data showed no change in assay, friability (<1%) and disintegration time.

Therefore the dispersible tablets of the present invention are not only stable at accelerated stability testing conditions but also are robust and can withstand the mechanical stress during packaging and transport.

A comparative, randomized two way Crossover bioavailability study was conducted on cephalexin 250 mg dispersible tablet (prepared as per the above example) formulation (T) and the commercially available Cephalexin (250mg/5mL) suspension formulation (R) of Eli Lilly in 34 healthy volunteers under fasting conditions. The pharmacokinetic data obtained was analyzed at and the 90% confidence interval (T/R) and the ratio of least square means T/R (%) was calculated as given in the following Table.

Table- Cephalexin dispersible tablet bio-profile in comparison to cephalexin oral suspension

	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
Ratio[1]	99.85%	99.85%	100.30%
90% Geometric C. I.[2]	97.81 to 101.93	97.86% to 01.88%	95.06% to 105.84%
Intra-Subject C.V.	5.03%	4.90	13.13%

The results of the study showed that 250 mg dispersible tablets of the present invention is bio-equivalent to cephalexin 250 mg/5mL oral suspension under fasting conditions.

[1] calculated using least-square means according to the formula:

$$e^{(T - R)} \times 100$$

[2] 90% Geometric confidence Interval using ln transformed data.

WE CLAIM:

1. A process for the preparation of water dispersible tablets of cephalexin, which disintegrate within 3 minutes in water at 20°C± 5°C to form a uniform suspension wherein the process comprises granulating cephalexin, conventional intragranular disintegrant(s) and colloidal silicon dioxide and optionally suspending/coloring agent with binder solution, of the kind as herein described; drying the resulting granules, mixing with conventional extragranular disintegrant(s), fillers, lubricating agents and optionally other excipients and compressing to form tablets; wherein the disintegrant comprises from 0.5% to 10%; colloidal silicon dioxide comprises from 0.25% to 6.0%; and binder comprises 0.25% to 4%; and lubricant comprises from 0.25% to 5% by weight of the total tablet weight.
2. The process according to claim 1 wherein other excipients are selected from antiadherants, sweeteners and flavoring agent.
3. The process according to claim 1 where cephalexin is present as monohydrate.
4. The process according to claim 1 wherein cephalexin has a particle size d_{90} <250μm.
5. The process according to claim 1 wherein the intra and extragranular disintegrant are selected from the group consisting of sodium starch glycolate, carboxy methylcellulose, croscarmellose sodium and cross-linked polyvinylpyrrolidone and combinations thereof.
6. The process according to claim 5 wherein the disintegrant is cross-linked polyvinylpyrrolidone.

7. The process according to claim 1 wherein the binder is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone and combinations thereof.

8. The process according to claim 7 wherein the binder is polyvinyl pyrrolidone.

9. The process according to claim 1 wherein the filler is selected from the group consisting of lactose, microcrystalline cellulose, mannitol and combinations thereof.

10. The process according to claim 1 wherein the lubricants may be selected from the group consisting of magnesium stearate, stearic acid or sodium stearyl fumarate and combinations thereof.

11. The process according to claim 1 wherein the suspending agent is selected from microcrystalline cellulose, sodium carboxy methylcellulose, colloidal silicon dioxide, mannitol, povidone, sodium starch glycolate or a combination thereof.

12. The process according to claim 1 wherein the suspending agent is present in an amount of about 0.25% to about 6.0% by weight of the total tablet weight.

13. The process according to claim 2 wherein the antiadherant is colloidal silicon dioxide.

14. The process according to claim 2 wherein the sweetening agent is selected from sugars, saccharin or its salts, aspartame or combinations thereof.

15. The process according to claim 2 wherein sweetening agent is present in an amount of about 0.01% to about 2.0% by weight of total weight of tablet.

16. The process according to claim 2 wherein the flavoring agent is Flavor Peppermint.

17. The process for the preparation of water dispersible tablet of cephalexin as exemplified herein.

Dated this 2ND day of **AUGUST**, 2002.

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary